

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202880Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Addendum

Date	September 19, 2013
From	Ellen Fields, MD, MPH
Subject	Cross-Discipline Team Leader Addendum
NDA/BLA #	202880
Supplement#	
Applicant	Zogenix, Inc
Date of Submission	May 1, 2012
PDUFA Goal Date	March 1, 2013
Proprietary Name / Established (USAN) names	Zohydro ER/Hydrocodone bitartrate extended-release capsules
Dosage forms / Strength	Capsules/10, 15, 20, 30, 40, or 50 mg
Proposed Indication(s)	Management of moderate to severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time
Recommended:	Approval

Introduction

Zogenix, Inc. submitted their NDA for Zohydro ER, hydrocodone extended-release capsules, on May 1, 2012. This application was submitted under Section 505(b)(2) of the Food, Drug, and Cosmetic Act, referencing in part the Agency's prior findings of safety and efficacy for Vicoprofen, NDA 20-716. The Applicant's proposed indication is for the "management of moderate to severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time." If approved, Zohydro ER would be the first approved, and the first marketed, single-entity hydrocodone product in the U.S. As a Schedule II drug product under the Controlled Substances Act (CSA), there would be additional restrictions on its prescribing and dispensing compared to the numerous approved hydrocodone combination drug products (e.g., Vicodin, Vicoprofen, multiple generic products) which fall under Schedule III of the CSA.

The NDA has been reviewed by all disciplines and the reviews completed in April, 2013 reflect their findings. Overall, the Applicant met the standards for approval of the NDA from the chemistry, preclinical, pharmacological, and clinical perspectives. The efficacy of Zohydro ER was demonstrated in a single adequate and well-controlled clinical trial in subjects with chronic low back pain, and the assessment of safety from the clinical trials showed that the safety profile appears similar to other approved extended-release opioid analgesics. There were no unexpected or unusual safety signals that were reported during Zohydro ER's clinical development. However, the decision was made at the time of the PDUFA date to delay the regulatory action on the NDA due to the reasons discussed below.

Details regarding the overall review of the NDA submission may be found in my CDTL Review dated January 31, 2013. This addendum discusses the reasons that led to the delayed regulatory

action, subsequent Agency activities, an updated discussion of the Advisory Committee meeting, and my recommendation for a regulatory action at this time.

Reasons for Delayed Regulatory Action

The delayed regulatory action for Zohydro ER is the result of ongoing Agency activities that are being carried out to help ensure safe and appropriate prescribing and effective and safe use of drug products in the ER/LA opioid class, including Zohydro ER.

The Agency has developed language for a class labeling change for all ER/LA opioid analgesics. The impetus for this change was the increasingly serious public health problem of prescription opioid abuse and misuse, and consequences that include addiction, overdose, and death. The Agency has received public input on this topic from a number of sources including citizen petitions, the Zohydro ER Advisory Committee Meeting held on December 7, 2012, and the Part 15 Hearing held February 7-8, 2013, on the impact of approved drug labeling on chronic opioid therapy. In a Center Director Briefing on February 6, 2013, issues related to the approval of new non-abuse deterrent, extended-release opioids in the environment of the worsening public health problem of prescription opioid misuse and abuse were discussed.

On September 10, 2013, DAAAP sent letters to sponsors of the ER/LA opioid analgesics requesting safety labeling changes and imposing postmarketing study requirements. The safety labeling changes will modify the ER/LA labeling in order to better delineate the risks and benefits to patients, and to assist prescribers in safe and appropriate prescribing of these products. Also included in the revised labeling is a modification of the indication for ER/LA opioids, so that it more clearly describes the target patient population in light of balancing both risks and benefits. A warning is also being added to the boxed warning regarding the risk of neonatal opioid withdrawal syndrome in infants of mothers who have used opioids chronically. The Zohydro ER labeling will incorporate the class-wide labeling. The postmarketing study requirements are being imposed in order to further assess the known risks associated with ER/LA opioid analgesics of abuse and misuse and their consequences, and to also assess the development of hyperalgesia associated with chronic opioid use.

In summary, the Agency is making efforts to ensure the safe and appropriate prescribing and safe use of ER/LA opioid analgesics via the new class safety labeling changes and the ER/LA class REMS that was approved in July, 2012, and to obtain further information on the known long-term risks of abuse and misuse and their consequences, and the development of hyperalgesia associated with chronic opioid use.

Advisory Committee Meeting

As discussed in my CDTL memo dated January 21, 2013, an Advisory Committee meeting was held in December, 2012 to discuss the Zohydro ER application.

At this meeting, the Office of Surveillance and Epidemiology presented drug utilization data along with data on emergency room visits related to oxycodone use comparing single-entity ER oxycodone with combination IR oxycodone products as one way to explore the potential for abuse following marketing of the first single-entity hydrocodone extended-release product. The

findings showed that the proportion of ER visits relative to the number of tablets dispensed (known as the abuse ratio) of single-ingredient ER oxycodone products is three- to four-fold higher than for combination IR oxycodone products. When interpreting this analysis, it is important to note the differences between the current environment for the introduction of Zohydro ER to the marketplace, and the environment that existed when extended-release oxycodone was approved in the mid- 1990's. OxyContin was approved in 1995, which was when the treatment of pain became an important aspect of medical care, and the assessment of pain became the "fifth vital sign." OxyContin was also promoted by industry as less abusable compared to IR oxycodone, which was untrue. In contrast, Zohydro ER will be entering the market during a time of heightened awareness of the risks abuse and misuse of prescription opioids, with more appropriate labeling and the ER/LA class REMS.

After deliberations, the committee agreed that the Applicant met the approval standards set forth by the Agency and stated that Zohydro ER is as safe as other long-acting and extended-release opioid analgesics that have previously been approved. However, the majority of the committee voted that the Zohydro ER NDA should not be approved (11 against approval, two in favor of approval, one abstention) because of the concerns regarding abuse and misuse for Zohydro ER as well as the already approved ER/LA opioid analgesics.

I disagree with the committee's conclusion, in that the benefit risk balance for the already approved non-abuse deterrent opioid analgesics and Zohydro ER remains favorable for patients requiring chronic opioid therapy. The products provide effective and safe treatment options for patients with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Controlled Substance Staff (CSS) Review

At the time of the January, 2013 CDTL memo writing, CSS had not finalized their review of the Zohydro ER NDA. The review entered into DARRTS on February 5, 2013, states that the Applicant did not include a systematic reporting of abuse, misuse, and diversion cases in the clinical trial protocols, and therefore the assessment of the full scope of abuse and misuse during clinical development was not possible. In the CSS review, they recommended that the sponsor "referred to the new CDER/FDA guidance on development of an abuse deterrent formulation of Zohydro ER, as a means to reduce the predictable high levels of abuse of the current formulation." CSS predicted "High levels of abuse, misuse, and addiction" based on the fact that the Zohydro ER formulation is not abuse-deterrent, comes in strengths from 10 to 50 mg, can be made to release hydrocodone easily for abuse by oral, intranasal or intravenous routes, and that in the future, the sponsor should conduct a better evaluation of misuse and abuse cases during development. While this is true, from the clinical perspective, Zohydro ER is a Schedule II opioid analgesic with known abuse potential. The risk for abuse and misuse of Zohydro ER is no greater than for other opioids in the ER/LA class that lack abuse-deterrent formulations, and does not outweigh the potential benefit of having this product available for properly selected patients with chronic pain. The assessment of abuse in the relatively small population of patients who participated in the clinical trials would not likely add useful information to what is already known regarding the abuse of Schedule II opioids, including Zohydro ER.

Zohydro ER labeling

The requested ER/LA opioid analgesic safety labeling changes have been reflected in the Zohydro ER label and are presented below (noting only sections that differ in wording from previous ER/LA labeling):

HIGHLIGHTS

BOXED WARNING

In the boxed warning in Highlights, include the following text:

- **Tradename exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient’s risk before prescribing, and monitor regularly for development of these behaviors or conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow Tradename (formulation) whole to avoid exposure to a potentially fatal dose of (active opioid). (5.2)**
- **Accidental consumption of Tradename, especially in children, can result in fatal overdose of (active opioid). (5.2)**
- **For patients who require opioid therapy while pregnant, be aware that infants may require treatment for neonatal opioid withdrawal syndrome. Prolonged use during pregnancy can result in life-threatening neonatal opioid withdrawal syndrome. (5.3)**

For products with an interaction with alcohol, also include the following:

- **Instruct patients not to consume alcohol or any products containing alcohol while taking Tradename because co-ingestion can result in fatal plasma (active opioid) levels. (5.4)**

INDICATIONS AND USAGE

Under this heading in Highlights, include the full text from this section of the Full Prescribing Information (plus the required pharmacologic class).

DOSAGE AND ADMINISTRATION

Under this heading in Highlights, include the following:

- For opioid-naïve and opioid non-tolerant patients, initiate with X mg (formulation) orally every X hours. (2.1)

For products for which a conversion table is available, include the following bullet.

- To convert to Tradename from another opioid, use available conversion factors to obtain estimated dose. (2.1)

If specific recommendations on a titration scheme are available, include the following bullet.

- Dose can be increased every X to X days, using increments of X mg every X hours (i.e., X mg per day). (2.2)

WARNINGS AND PRECAUTIONS

Under this heading in Highlights, include the following:

- Interactions with CNS depressants: Concomitant use may cause profound sedation, respiratory depression, and death. If coadministration is required, consider dose reduction of one or both drugs. (5.4)
- Elderly, cachectic, debilitated patients, and those with chronic pulmonary disease: Monitor closely because of increased risk for life-threatening respiratory depression. (5.5, 5.6)

TABLE OF CONTENTS

Update the **TABLE OF CONTENTS** to reflect the changes in the **FULL PRESCRIBING INFORMATION**.

FULL PRESCRIBING INFORMATION

BOXED WARNING

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; NEONATAL OPIOID WITHDRAWAL SYNDROME; and INTERACTION WITH ALCOHOL (*last warning only for products that have an interaction with alcohol*)

Addiction, Abuse, and Misuse

Tradename exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Tradename, and monitor all patients regularly for the development of these behaviors or conditions [*see Warnings and Precautions (5.1)*].

Life-threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of Tradename. Monitor for respiratory depression, especially during initiation of Tradename or following a dose increase. Instruct patients to swallow Tradename (formulation; e.g., tablets, capsules) whole; crushing, chewing, or dissolving Tradename (formulation) can cause rapid release and absorption of a potentially fatal dose of (active opioid) [*see Warnings and Precautions (5.2)*].

Accidental Exposure

Accidental consumption of even one dose of Tradename, especially by children, can result in a fatal overdose of (active opioid) [*see Warnings and Precautions (5.2)*].

Neonatal Opioid Withdrawal Syndrome

For patients who require opioid therapy while pregnant, be aware that infants may require treatment for neonatal opioid withdrawal syndrome. Prolonged maternal use of Tradename during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening and requires management according to protocols developed by neonatology experts [see Warnings and Precautions (5.3)].

Interaction with Alcohol *(This subheading and text should be included in the boxed warning only for products that have an interaction with alcohol.)*

Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking Tradename. The co-ingestion of alcohol with Tradename may result in increased plasma levels and a potentially fatal overdose of (active opioid) [see Warnings and Precautions (5.4)].

1 INDICATIONS AND USAGE

Tradename is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Tradename for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- Tradename is not indicated as an as-needed (prn) analgesic.

2 DOSAGE AND ADMINISTRATION

2.1 Initial Dosing

Tradename should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

Initiate the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience and risk factors for addiction, abuse, and misuse [see Warnings and Precautions (5.1)]. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with Tradename [see Warnings and Precautions (5.2)].

Tradename (formulation) must be taken whole, one (formulation) at a time, with enough water to ensure complete swallowing immediately after placing in the mouth [see Patient Counseling Information (17)]. Crushing, chewing, or dissolving Tradename (formulation) will result in

uncontrolled delivery of (active opioid) and can lead to overdose or death [see *Warnings and Precautions (5.2)*].

Use of Tradename as the First Opioid Analgesic

Initiate treatment with Tradename with X mg (formulation) orally every X hours.

Use of Tradename in Patients who are not Opioid Tolerant

The starting dose for patients who are not opioid tolerant is Tradename X mg orally every X hours. Patients who are opioid tolerant are those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, or an equianalgesic dose of another opioid.

Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression.

Conversion from Other Oral Opioids to Tradename

Discontinue all other around-the-clock opioid drugs when Tradename therapy is initiated.

For products with existing conversion data, include the following information on conversion: Although tables of oral and parenteral equivalents are readily available, there is substantial inter-patient variability in the relative potency of different opioid drugs and products. As such, it is preferable to underestimate a patient's 24-hour oral (active opioid) requirements and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour oral (active opioid) requirements and manage an adverse reaction. In a Tradename clinical trial with an open-label titration period, patients were converted from their prior opioid to Tradename using the Table 1 as a guide for the initial Tradename dose.

Consider the following when using the information in Table 1:

- This is **not** a table of equianalgesic doses.
- The conversion factors in this table are only for the conversion **from** one of the listed oral opioid analgesics **to** Tradename.
- The table **cannot** be used to convert **from** Tradename **to** another opioid. Doing so will result in an overestimation of the dose of the new opioid and may result in fatal overdose.

Table 1. Conversion Factors to Tradename

Prior Oral Opioid	Approximate Oral Conversion Factor

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To calculate the estimated Tradename dose using Table 1:

- For patients on a single opioid, sum the current total daily dose of the opioid and then multiply the total daily dose by the conversion factor to calculate the approximate oral (active opioid) daily dose.

If the product's total daily dose is to be given in divided doses, describe here immediately following the sentence above (e.g., The daily dose should then be divided in half for administration every 12 hours.)

- For patients on a regimen of more than one opioid, calculate the approximate oral (active opioid) dose for each opioid and sum the totals to obtain the approximate total (active opioid) daily dose.

If the product's total daily dose is to be given in divided doses, describe here immediately following the sentence above (e.g., The daily dose should then be divided in half for administration every 12 hours.)

- For patients on a regimen of fixed-ratio opioid/non-opioid analgesic products, use only the opioid component of these products in the conversion.

Always round the dose down, if necessary, to the appropriate Tradename strength(s) available.

Example conversion from a single opioid to Tradename:

Step 1: Sum the total daily dose of the opioid (in this case, *insert name and dosage regimen of example former opioid*)

XX mg former opioid X times daily = XX mg total daily dose of former opioid

Step 2: Calculate the approximate equivalent dose of oral (active opioid) based on the total daily dose of the current opioid using Table 1

XX mg total daily dose of former opioid x Conversion Factor = XX mg of oral (active opioid) daily

Step 3: Calculate the approximate starting dose of Tradename to be given every X hours. Round down, if necessary, to the appropriate Tradename (formulation) strengths available.

XX mg Tradename every X hours

Close observation and frequent titration are warranted until pain management is stable on the new opioid. Monitor patients for signs and symptoms of opioid withdrawal or for signs of over-sedation/toxicity after converting patients to Tradename.

For products that do not have conversion tables, include instructions for conversion from other opioids or if all patients are to be titrated from the lowest dose when switched to this product.

Conversion from Methadone to Tradename

Close monitoring is of particular importance when converting from methadone to other opioid agonists. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and can accumulate in the plasma.

If any other product-specific conversion instructions are available, insert them here.

2.2 Titration and Maintenance of Therapy

Individually titrate Tradename to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving Tradename to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for opioid analgesics.

If specific recommendations on a titration scheme are available, insert here (e.g., Increase the dose of Tradename every X to X days as needed to achieve adequate analgesia, using increments of X mg every X hours.)

Patients who experience breakthrough pain may require a dose increase of Tradename, or may need rescue medication with an appropriate dose of an immediate-release analgesic. If the level of pain increases after dose stabilization, attempt to identify the source of increased pain before increasing the Tradename dose.

If unacceptable opioid-related adverse reactions are observed, the subsequent doses may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse (Replaces subsection “Abuse Potential”)

Tradename contains (active opioid), a Schedule II controlled substance. As an opioid, Tradename exposes users to the risks of addiction, abuse, and misuse [*see Drug Abuse and Dependence (9)*]. As modified-release products such as Tradename deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of (active opioid) present.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed Tradename and in those who obtain the drug illicitly. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing Tradename, and monitor all patients receiving Tradename for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol addiction or abuse) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the prescribing of Tradename for the proper management of pain in any given patient. Patients at increased risk may be prescribed modified-release opioid formulations such as Tradename, but use in such patients necessitates intensive counseling about the risks and proper use of Tradename along with intensive monitoring for signs of addiction, abuse, and misuse.

Abuse or misuse of Tradename by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the (active opioid) and can result in overdose and death [*see Overdosage (10)*].

5.2 Life-threatening Respiratory Depression (Now incorporates subsection "Accidental Exposure")

Serious, life-threatening, or fatal respiratory depression has been reported with the use of modified-release opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status [*see Overdosage (10)*]. Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of Tradename, the risk is greatest during the initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with Tradename and following dose increases.

To reduce the risk of respiratory depression, proper dosing and titration of Tradename are essential [*see Dosage and Administration (2)*]. Overestimating the Tradename dose when converting patients from another opioid product can result in fatal overdose with the first dose.

Accidental consumption of even one dose of Tradename, especially by children, can result in respiratory depression and death due to an overdose of (active opioid).

5.3 Neonatal Opioid Withdrawal Syndrome (New)

For patients who require opioid therapy while pregnant, be aware that infants may require treatment for neonatal opioid withdrawal syndrome. Prolonged maternal use of Tradename during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening and requires management according to protocols developed by neonatology experts.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

5.4 Interactions with Central Nervous System Depressants (Replaces subsections “Interactions with CNS Depressants and Illicit Drugs” and “Interactions with Alcohol”)

Include this paragraph only for products that have an interaction with alcohol.

Patients must not consume alcoholic beverages or prescription or non-prescription products containing alcohol while on Tradename therapy. The co-ingestion of alcohol with Tradename may result in increased plasma levels and a potentially fatal overdose of (active opioid) [see *Clinical Pharmacology (12.3)*].

Hypotension, profound sedation, coma, respiratory depression, and death may result if Tradename is used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids).

When considering the use of Tradename in a patient taking a CNS depressant, assess the duration use of the CNS depressant and the patient’s response, including the degree of tolerance that has developed to CNS depression. Additionally, evaluate the patient’s use of alcohol or illicit drugs that cause CNS depression. If the decision to begin Tradename is made, start with Tradename X mg every X hours, monitor patients for signs of sedation and respiratory depression, and consider using a lower dose of the concomitant CNS depressant [see *Drug Interactions (7.x)*].

5.5 Use in Elderly, Cachectic, and Debilitated Patients

Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating Tradename and when Tradename is given concomitantly with other drugs that depress respiration [see *Warnings and Precautions (5.2)*].

7 DRUG INTERACTIONS

7.1 Alcohol (*Include this subsection for products with an interaction with alcohol.*)

Concomitant use of alcohol with Tradename can result in an increase of (active opioid) plasma levels and potentially fatal overdose of (active opioid). Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol while on Tradename therapy [see [Clinical Pharmacology \(12.3\)](#)].

7.X CNS Depressants

The concomitant use of Tradename with other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol can increase the risk of respiratory depression, profound sedation, coma and death. Monitor patients receiving CNS depressants and Tradename for signs of respiratory depression, sedation and hypotension.

When combined therapy with any of the above medications is considered, the dose of one or both agents should be reduced [*see Dosage and Administration (2.2) and Warnings and Precautions (5.4)*].

7.X Drugs Affecting Cytochrome P450 Isoenzymes (Include subsection only for products that have an effect on cytochrome P450 isoenzymes)

Inhibitors of CYP3A4 and (b) (4)

Because the CYP3A4 isoenzyme plays a major role in the metabolism of (active opioid), drugs that inhibit CYP3A4 activity may cause decreased clearance of (active opioid) which could lead to an increase in (active opioid) plasma concentrations and result in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of (b) (4) and 3A4 inhibitors. If co-administration with Tradename is necessary, monitor patients for respiratory depression and sedation at frequent intervals and consider dose adjustments until stable drug effects are achieved [*see Clinical Pharmacology (12.3)*].

Inducers of CYP3A4

CYP450 3A4 inducers may induce the metabolism of (active opioid) and, therefore, may cause increased clearance of the drug which could lead to a decrease in (active opioid) plasma concentrations, lack of efficacy or, possibly, development of a withdrawal syndrome in a patient who had developed physical dependence to (active opioid). If co-administration with Tradename is necessary, monitor for signs of opioid withdrawal and consider dose adjustments until stable drug effects are achieved [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome [*see Warnings and Precautions (5.3)*].

Teratogenic Effects - Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Tradename should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Follow with drug-specific nonclinical data.

17 PATIENT COUNSELING INFORMATION

Addiction, Abuse, and Misuse

Inform patients that the use of Tradename, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose or death [see *Warnings and Precautions (5.1)*]. Instruct patients not to share Tradename with others and to take steps to protect Tradename from theft or misuse.

Life-threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting Tradename or when the dose is increased, and that it can occur even at recommended doses [see *Warnings and Precautions (5.2)*]. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Consumption

Inform patients that accidental exposure, especially in children, may result in respiratory depression or death [see *Warnings and Precautions (5.2)*]. Instruct patients to take steps to store Tradename securely and to dispose of unused Tradename by flushing the (formulation) down the toilet.

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that chronic use of Tradename during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening [see *Warnings and Precautions (5.3)*].

Interactions with Alcohol and other CNS Depressants

For products with an interaction with alcohol, include the following as the first paragraph under this subheading:

Instruct patients not to consume alcoholic beverages, as well as prescription and over-the counter products that contain alcohol, during treatment with Tradename. The co-ingestion of alcohol with Tradename may result in increased plasma levels and a potentially fatal overdose of (active opioid) [see *Warnings and Precautions (5.4)*].

Inform patients that potentially serious additive effects may occur if Tradename is used with alcohol or other CNS depressants, and not to use such drugs unless supervised by a health care provider.

The class ER/LA medication guide is included in the Zohydro ER labeling.

Medication Guide

TRADENAME (phonetic pronunciation) (drug substance) Drug formulation, CII

TRADENAME is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily around-the-clock, long-term treatment with an opioid, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.
- Not for use to treat pain that is not around-the-clock.

Important information about TRADENAME:

- **Get emergency help right away if you take too much TRADENAME (overdose).** When you first start taking TRADENAME, when your dose is changed, or if you take too much (overdose), serious or life threatening breathing problems that can lead to death may occur.
- Never give anyone your TRADENAME. They could die from taking it. Store TRADENAME away from children and in a safe place to prevent stealing or abuse. Selling or giving away TRADENAME is against the law.

Do not take TRADENAME if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking TRADENAME, tell your healthcare provider if you have a history of:

- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** TRADENAME may harm your unborn baby. Long-term (chronic) use during pregnancy can cause life-threatening withdrawal symptoms in your newborn baby.
- **breastfeeding.** TRADENAME passes into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking TRADENAME with certain other medicines can cause serious side effects.

When taking TRADENAME:

- Do not change your dose. Take TRADENAME exactly as prescribed by your healthcare provider.
- Take your prescribed dose every x hours, at the same time every day. Do not take more than your prescribed dose in x hours. If you miss a dose, take your next dose at your usual time the next day.
- Do not cut, break, chew, crush, dissolve, snort, or inject TRADENAME because this may cause you to overdose and die.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking TRADENAME without talking to your healthcare provider.**

- After you stop taking TRADENAME, flush any unused tablets down the toilet.

While taking TRADENAME DO NOT:

- Drive or operate heavy machinery until you know how TRADENAME affects you. TRADENAME can make you sleepy, dizzy, or lightheaded.
- Drink alcohol, or use prescription or over-the-counter medicines containing alcohol. Using products containing alcohol during treatment with TRADENAME may cause you to overdose and die.

The possible side effects of TRADENAME are:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat, extreme drowsiness, low blood pressure when changing positions, or you are feeling faint.

These are not all the possible side effects of TRADENAME. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to**

dailymed.nlm.nih.gov

Regulatory Action

Approval

Given the 1) safety labeling changes to the ER/LA opioid analgesics and the ER/LA REMS, 2) that the Zohydro ER application has met the regulatory requirements for approval of an extended-release opioid analgesic, 3) patients with chronic pain requiring long-term opioid therapy can benefit from having the option for an extended-release hydrocodone product, and 4) because the benefit/risk balance of Zohydro ER is similar to that of already approved ER/LA opioid analgesics, I recommend approval of this NDA. As discussed in my original memo, there is no policy that precludes approval of an ER/LA opioid analgesic without an abuse-deterrent formulation as long as the overall benefit of that product outweighs the risks. Further contributing to the favorable balance of benefit and risk for Zohydro ER is not just the lack of any existing hydrocodone extended-release analgesic products, but, the lack of an approved abuse-deterrent hydrocodone extended-release analgesic.

Zohydro ER is the first single-entity hydrocodone product and the first extended-release hydrocodone product to be approved by the Agency. Prescribers will have the option of prescribing hydrocodone for patients who require an extended-release opioid, which is important for several reasons. First, individual patients can respond differently to different opioids. A given patient may experience varied benefit and adverse event profiles from one opioid

compared to another. Also, due to the development of tolerance to the beneficial effects of opioids over time, a common clinical strategy is to rotate the patient from one opioid to another. Zohydro ER provides an additional available opioid to which prescribers can switch patients if medically appropriate. Also, prescribers will now have the option of moving a patient who is responding well to an immediate-release hydrocodone combination product but who would benefit from treatment with an extended-release opioid to an extended-release hydrocodone product, obviating the need to switch the patient to a drug product with a different active ingredient. Next, because Zohydro ER is a single-entity product, prescribers may titrate Zohydro ER for individual patients without the limitations or toxicity concerns associated with the non-opioid active ingredient (e.g., acetaminophen) present in all other approved hydrocodone products. Finally, there are, as yet, no available hydrocodone products (single-entity or combination) with abuse-deterrent properties. It is important to consider the availability of alternative products when assessing the benefit/risk balance. Unlike the situation with OxyContin, where an abuse-deterrent formulation was approved and shown to have meaningful abuse-deterrent properties as reflected in product labeling, led to the removal of the original OxyContin formulation from the market for reasons of safety (increased potential for abuse compared to the reformulated version), there are no approved abuse-deterrent formulations of extended-release hydrocodone. Accordingly, for all of the above reasons, I have concluded that Zohydro ER's benefits currently outweigh its risks despite its lack of abuse-deterrent properties.

If at some point in the future, an abuse-deterrent, extended-release formulation of hydrocodone is approved and marketed with labeling that includes abuse-deterrent claims, the safety of Zohydro ER as it relates to the public health can be revisited by the Agency.

Post Marketing Requirements

The following are the post marketing requirements for Zohydro ER, the same as the requirements recently imposed on all ER/LA opioid analgesic sponsors. As these studies further evaluate the known risks of ER/LA opioid analgesics for abuse and misuse and their consequences, no new safety signals arose during the development of Zohydro ER, and considerable data exist on the safety of hydrocodone (used in combination with nonopioid analgesics for pain management for decades), studies to obtain the information described below may be conducted as post marketing studies.

2065-1 Conduct one or more studies to provide quantitative estimates of the serious risks of misuse, abuse, addiction, overdose, and death associated with long-term use of opioid analgesics for management of chronic pain, among patients prescribed ER/LA opioid products. Include an assessment of risk relative to efficacy.

These studies should address at a minimum the following specific aims:

- a. Estimate the incidence of misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain. Stratify misuse and overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of misuse, abuse, addiction, overdose, and death.
- b. Evaluate and quantify other risk factors for misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships. Stratify misuse and overdose by intentionality wherever possible.

The following timetable proposes the schedule by which you will conduct these studies:

Final Protocol Submission: 08/2014
Study Completion: 01/2018
Final Report Submission: 06/2018

2065-2 Develop and validate measures of the following opioid-related adverse events: misuse, abuse, addiction, overdose and death (based on DHHS definition, or any agreed-upon definition), which will be used to inform the design and analysis for PMR # 2065-1 and any future post-marketing safety studies and clinical trials to assess these risks. This can be achieved by conducting an instrument development study or a validation study of an algorithm based on secondary data sources.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: 08/2014
Study Completion: 08/2015
Final Report Submission: 11/2015

2065-3 Conduct a study to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the following opioid-related adverse events: misuse, abuse, addiction, overdose, and death in any existing post-marketing databases to be employed in the studies. Stratify misuse and overdose by intentionality wherever possible. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: 08/2014
Study Completion: 08/2015
Final Report Submission: 11/2015

2065-4 Conduct a study to define and validate “doctor/pharmacy shopping” as outcomes suggestive of misuse, abuse and/or addiction. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: 08/2014
Study Completion: 08/2015
Final Report Submission: 11/2015

The Agency determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risk of hyperalgesia³ associated with the class of ER/LA opioids, of which Zohydro ER is a member.

2065-5 Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following use of ER/LA opioid analgesics for at least one year to treat chronic pain. We strongly encourage you to use the same trial to assess the development of tolerance following use of ER/LA opioid analgesics. Include an assessment of risk relative to efficacy.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: 08/2014
Trial Completion: 08/2016
Final Report Submission: 02/2017

Sponsors of the ER/LA opioid analgesic NDAs are encouraged to work together to conduct these studies.

The following are postmarketing requirements for pediatric studies under PREA:

2066-1 Deferred pediatric study under PREA: Conduct a pharmacokinetic and safety study of an age-appropriate formulation of hydrocodone extended-release in patients from ages 12 to less than 17 years with moderate-to-severe pain requiring around the clock opioid therapy for an extended period of time.

Final Protocol Submission: August 31, 2014
Study/Trial Completion: February 28, 2019
Final Report Submission: August 31, 2019

2066-2 Deferred pediatric study under PREA: Conduct a pharmacokinetic and safety study of an age-appropriate formulation of hydrocodone extended-release in patients from ages 7 to less than 12 years with moderate-to-severe pain requiring around the clock opioid therapy for an extended period of time.

Final Protocol Submission: August 31, 2017
Study/Trial Completion: August 31, 2021
Final Report Submission: February 28, 2022

Non-Clinical PMRs

2066-1 Conduct an in vivo comet assay in liver to evaluate the potential genetic toxicology of hydrocodone.

Final Protocol Submission: Protocol acceptable, study in progress
Study/Trial Completion: October 1, 2013
Final Report Submission: December 1, 2013

2066-2 Conduct a 2-year bioassay in the rat model to evaluate the carcinogenic potential of hydrocodone.

Final Protocol Submission: Protocol acceptable, study in progress
Study/Trial Completion: January 15, 2014
Final Report Submission: June 30, 2015

2066-3 Conduct a 2-year bioassay in the mouse model to evaluate the carcinogenic potential of hydrocodone.

Final Protocol Submission: Protocol acceptable, study in progress
Study/Trial Completion: January 24, 2014
Final Report Submission: June 30, 2015

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLEN W FIELDS
09/19/2013

Cross-Discipline Team Leader Review

Date	January 31, 2013
From	Ellen Fields, MD, MPH
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	202880
Supplement#	
Applicant	Zogenix, Inc
Date of Submission	May 1, 2012
PDUFA Goal Date	March 1, 2013
Proprietary Name / Established (USAN) names	Zohydro ER/Hydrocodone bitartrate extended-release capsules
Dosage forms / Strength	Capsules/10, 15, 20, 30, 40, or 50 mg
Proposed Indication(s)	Management of moderate to severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time
Recommended:	Approval

1. Introduction

On April 30, 2012, Zogenix, submitted a New Drug Application for hydrocodone bitartrate extended-release capsules (Zohydro ER), under section 505(b)(2) of the Food, Drug, and Cosmetic Act, based, in part, on the Agency's prior findings of safety and efficacy for Vicoprofen (hydrocodone bitartrate/ibuprofen tablets, NDA 20-716). The proposed indication is the management of moderate-to-severe chronic pain when a continuous around-the-clock opioid analgesic is needed for an extended period of time. Zohydro ER is unique in that it is the first single-entity hydrocodone analgesic product seeking approval in the United States.

Zohydro ER is an extended-release Schedule II opioid analgesic with no abuse-deterrent properties, that falls within the class of drugs that are part of the Extended-Release/Long-Acting (ER/LA) Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS), and the proposed indication is the same as that for other extended-release opioid analgesics. The application was presented to the Anesthetic and Analgesic Drug Product Advisory Committee on December 7, 2012, because, while the Division did not question the Applicant's efficacy and safety findings for Zohydro ER, committee's opinion was sought on whether they believed that, in the current environment of increasing prescription opioid abuse, the benefit-risk balance for this product was favorable, and whether the ER/LA REMS is sufficient to address its abuse liability in the postmarketing setting.

This review will include a discussion of the Advisory Committee proceedings and areas of concern regarding the approval of a new extended-release opioid that does not have abuse-deterrent properties. At this writing, there is neither a regulatory nor Agency policy that prohibits the approval of long-acting or extended-release opioids that do not possess abuse-deterrent properties, and the ER/LA REMS has been created in order to ensure safe use and mitigate risks of misuse and abuse of these products. However, regardless of the REMS, it can

be anticipated that a single-entity extended-release hydrocodone product will contribute to the already critical public health problem of prescription opioid misuse and abuse. It is also important to recognize that this new product may be a useful addition to the armamentarium of analgesics that treat the serious and undertreated condition of chronic pain in the US.

2. Background

On May 1, 2012, the Agency received the NDA for Zohydro ER seeking approval for the management of moderate-to-severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time in adults. As stated above, this is the first single-entity, extended-release hydrocodone product submitted for Agency approval. The hydrocodone drug substance is listed in Schedule II of the Controlled Substances Act (CSA). Hydrocodone is currently available as an analgesic only as a combination product with non-narcotic analgesics such as ibuprofen, acetaminophen, and aspirin. According to the CSA, Schedule III controls apply to hydrocodone combination products containing no more than 300 milligrams per 100 milliliters or not more than 15 milligrams of hydrocodone base per dosage unit, with one or more active non-narcotic ingredients in recognized therapeutic amounts. All currently approved combination hydrocodone products fall under Schedule III, while Zohydro ER, as a single-entity product, would be regulated under Schedule II.

The Applicant's product is a 12-hour extended-release formulation of hydrocodone that utilizes Alkermes' patented Spheroidal Drug Absorption System (SODAS®) drug delivery technology. The proposed dosage strengths are 10, 15, 20, 30, 40, and 50mg capsules.

Information submitted in the NDA includes Chemistry Manufacturing and Control data (CMC), nonclinical studies (acute and repeat-dose toxicology, developmental, and reproductive toxicology), clinical pharmacology data, including six Phase 1 studies and two Phase 2 studies, in vitro abuse liability studies, and the results of Phase 3 efficacy and safety studies.

As a 505(b)(2) application relying on prior findings of safety and efficacy for Vicoprofen (NDA 20-716), the Division requested and the Applicant submitted one principal study to support the efficacy of Zohydro ER. Study ZX002-0801 was a randomized, placebo-controlled study with an open-label conversion/titration (C/T) phase of Zohydro ER followed by a randomized double-blind 12-week treatment phase of Zohydro ER vs. placebo in subjects with moderate-to-severe chronic low back pain (CLBP). Study ZX002-0802 was an open-label study with treatment up to 52 weeks with Zohydro ER, that enrolled both subjects from the Phase 3 efficacy study and de novo patients. Exposure to Zohydro ER included approximately 1500 subjects, with 332 exposed for at least 6 months and 290 for at least one year.

Along with adequate evidence of efficacy and safety for Zohydro ER, an important part of the review of this application has involved the advice provided by the Advisory Committee. The Agency presentations at the meeting included usage data for hydrocodone combination products and epidemiologic data on the abuse of hydrocodone combination products compared to the abuse of other opioid combination products in order to provide some perspective on the potential abuse risk of Zohydro ER. Data was also presented on abuse liability studies of single-entity hydrocodone performed by academic investigators. This information will be

discussed in this review in Section 9, and will enter into my conclusions regarding the risk-benefit balance for Zohydro ER.

3. CMC/Device

The CMC review was conducted by Yong Hu, Ph.D., with secondary concurrence from Prasad Peri, Ph.D. The review team has recommended approval from the CMC perspective.

Drug Substance

The Applicant proposes to use the hydrocodone bitartrate drug substance sourced from both (b) (4) (DMF (b) (4) and (b) (4) (DMF (b) (4) however, only the (b) (4)-sourced drug product is acceptable because the (b) (4) DMF does not show adequate manufacturing capability and product specification to control impurities below the more stringent ICH qualification threshold for a drug product with > 2 g total daily dose. DAAAP advised the CMC team that the maximum daily dose of hydrocodone bitartrate would be up to 3 grams since the dosing of a single-entity product is not limited by the non-opioid analgesic present in combination hydrocodone products. The drug product manufacturer, Alkermes, has committed to not using the (b) (4) drug substance.

The (b) (4) DMF is adequate. (b) (4) manufactures the drug substance in their (b) (4) or (b) (4) facilities, which have been deemed acceptable by the Office of Compliance. The Applicant has agreed to use only the (b) (4) drug substance.

Drug Product

As stated in Dr. Hu's review:

Hydrocodone bitartrate extended-release (hydrocodone-ER) capsule (also named ELN154088 in some development documentation), is an extended-release capsule product using Alkermes' Spheroidal Oral Drug Absorption System (SODAS[®]) technology. With this technology the sugar spheres are initially coated with the drug substance and other suitable excipients to form immediate-release (IR) multiparticulates (beads). Sustained-release (SR) multiparticulates (beads) are then prepared by coating the IR beads with a rate-controlling polymer (ammonio methacrylate copolymer (b) (4)

(b) (4) The extended-release product is then achieved by combining IR beads with SR beads in a defined dosage ratio (20:80 w/w) followed by encapsulation to the desired product strength of 10, 15, 20, 30, 40, or 50 mg of hydrocodone bitartrate in hard gelatin capsules. It should be noted that all the capsule strengths (b) (4)

(b) (4) The excipients include sugar spheres, hypromellose, silicon dioxide, and talc in addition to the ammonio methacrylate copolymer (b) (4) The capsule shells contain titanium dioxide, FD&C Blue #1, FD&C Red #40, FDA Yellow iron oxide, FD&C Red #3, FDA Black iron oxide, FDA Red iron oxide, and gelatin. The drug product is manufactured by Alkermes Gaineville LLC (former Elan Holdings) in their

Gaineville, Georgia facility, which has been deemed acceptable by the Office of Compliance.

Other CMC information

The Applicant requested a biowaiver for the 15mg strength. The biopharmaceutics reviewer agreed with the CMC team that the biowaiver request is acceptable based on (b) (4) and the 15mg showed comparable batch analysis to the other strengths.

The rate-controlling polymer ammonio methacrylate copolymer (b) (4) is soluble in alcohol, therefore the extended-release characteristics of the product may be compromised in the presence of alcohol. This is discussed further in the clinical pharmacology section.

The drug product does not have any abuse-deterrent properties by design. The in vitro abuse liability study demonstrated that the drug can be extracted from the product using a variety of solvents including water, dilute acid and base, and ethanol. Physical manipulation of the product (grinding and chewing) breaks down the polymer coating and can facilitate the extraction of drug substance from the product.

The capsules are supplied in (b) (4)-count or 100-count HDPE bottles with a child-resistant closure. The product is stored at 25° C (77° F); excursions permitted to 15°–30° C (59°–86° F). [See USP Controlled Room Temperature]. The proposed (b) (4) expiration dating period for the (b) (4)-count and 24 months for the 100-count bottles are acceptable.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology review was conducted by Elizabeth Bolan, Ph.D., with secondary concurrence by R. Daniel Mellon, Ph.D. There were no issues identified by the review team that preclude approval of Zohydro ER.

As stated in Dr. Bolan's review, the excipients, when calculated for the maximum theoretical daily dose of hydrocodone, can all be found in previously approved products and do not present any unique toxicologic concerns. All impurities/degradants in the drug substance and drug product are controlled at acceptable levels. Hydrocodone-related toxicities in acute and repeat-dose general toxicology studies were consistent with the known toxicities of other opioid agonists.

The standard ICH battery of genetic toxicology studies was conducted. Hydrocodone tested negative in the in vitro bacterial reverse mutation assay, the in vivo mouse micronucleus assay, and the in vitro chromosome aberration assay in the absence of metabolic activation. In contrast, hydrocodone tested positive for clastogenic activity in the in vitro chromosome aberration assay in the presence of metabolic activation. Hydrocodone is considered to have clastogenic potential and a fourth test will be required to be conducted post-marketing. Carcinogenicity assessments in mice and rats with hydrocodone are currently being conducted by the Applicant and will be submitted to the NDA as a post-marketing requirement (PMR). At the time of this review, the results of the two carcinogenicity assessments are not available.

As stated in Dr. Bolan's review, a full battery of developmental and reproductive toxicology studies has been conducted with hydrocodone. Decreases in female fertility were observed at all doses tested in the fertility study. No NOAEL was established for effects on female fertility, the lowest dose tested was two-times the human dose of 100 mg/day on a mg/m² basis. However, the changes in fertility observed in the rat may be related to known opioid-mediated effects on prolactin, which is essential for estrous cycling in the rat. The clinical relevance of the fertility finding is not known. No effects of hydrocodone on male fertility parameters were observed (NOAEL is ten-times the human dose of 100 mg/day on a mg/m² basis), however, decreased weights of male reproductive organs were observed at all doses. No effects of hydrocodone were seen in a rat embryofetal development study at any dose tested, although hydrocodone-mediated decreases in fertility limited the dosing in the study (NOAEL is approximately two-times the human dose of 100 mg/day on a mg/m² basis). In the rabbit embryofetal development study, fetal body weights were significantly decreased in all treated groups. Increases in the number of fetal malformations, including umbilical hernia and various irregularly shaped bones (ulna, femur, tibia, fibula) were observed in the highest dose group. Decreases in the number of ossified hyoid bodies and xiphoid bones, considered a developmental variation, were also observed in the highest dose group. The NOAEL for teratogenicity in the rabbit study is ten-times the human dose of 100 mg/day on a mg/m² basis. In the peri- and post-natal study, hydrocodone-mediated decreases on pup body weights, viability and lactation indices were observed (NOAEL is 0.5-times the human dose of 100 mg/day on a mg/m² basis). A pregnancy category C is recommended for this product and the relevant results will be described in the label.

The recommendation from the pharmacology/toxicology team is that this NDA be approved with PMRs to conduct an additional fourth tier genetic toxicology study and complete the two ongoing carcinogenicity studies (mouse and rat) with hydrocodone bitartrate. Specific labeling changes proposed by the pharmacology/toxicology team are noted in Dr. Bolan's review.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review was conducted by David Lee, Ph.D., with secondary concurrence by Yun Xu, Ph.D.

The biopharmaceutics review was conducted by Minerva Hughes, Ph.D. with secondary concurrence by John Duan, Ph.D., Angelica Dorantes, Ph.D., and Richard Lostritto, Ph.D.

Both groups have recommended approval of Zohydro ER from their respective perspectives.

Clinical Pharmacology

The clinical pharmacology information in this NDA submission included six Phase 1 studies and two Phase 2 studies. Additionally, the Applicant conducted a population pharmacokinetic (PK) analysis using the information observed from conducted studies to support the hydrocodone dose linearity purpose. The following is a summary of Dr. Lee's review.

Relative Bioavailability (Study ZX002-1102)

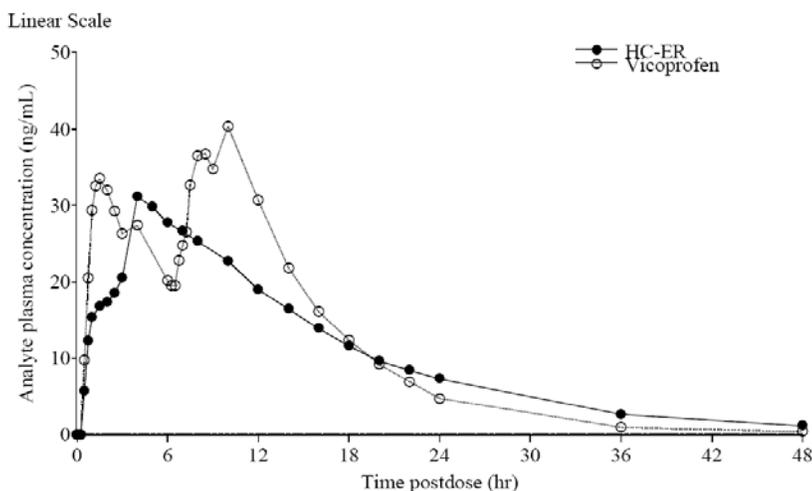
This was a Phase 1, open-label, randomized, two-dose, two-period cross-over study with minimum 5-day washout between treatments. The study was conducted in 15 healthy subjects between 18 and 45 years of age who received a single dose of 30 mg Zohydro ER and two consecutive doses of 2-tablets of Vicoprofen 6 hours apart for a total of 4 tablets. Subjects were fasted appropriately for both treatment groups. All doses were administered with 240 mL of ambient temperature water.

Mean hydrocodone C_{max} values were 32 ± 7 and 46 ± 7 ng/mL for Zohydro ER and Vicoprofen treatments, respectively. Mean hydrocodone C_{max} were not similar between the two treatments as indicated by the bioequivalence evaluation. Although Zohydro ER has both IR and ER characteristics, it is not surprising that it was not bioequivalent for C_{max} when compared to a product with only IR characteristics.

Mean hydrocodone AUC values were 513 ± 92 and 559 ± 122 ng.h/mL for Zohydro ER and Vicoprofen treatments, respectively. The bioequivalence analysis indicated that the AUC values from the two treatments were equivalent.

The following figure taken from page 59 of Dr. Lee's review is a graphic representation of the relative BA results:

Figure 2: Mean Hydrocodone Concentrations at Scheduled Time Points, Stratified by Treatment



Source: [Section 14, Figure 14.2.1-1a](#)

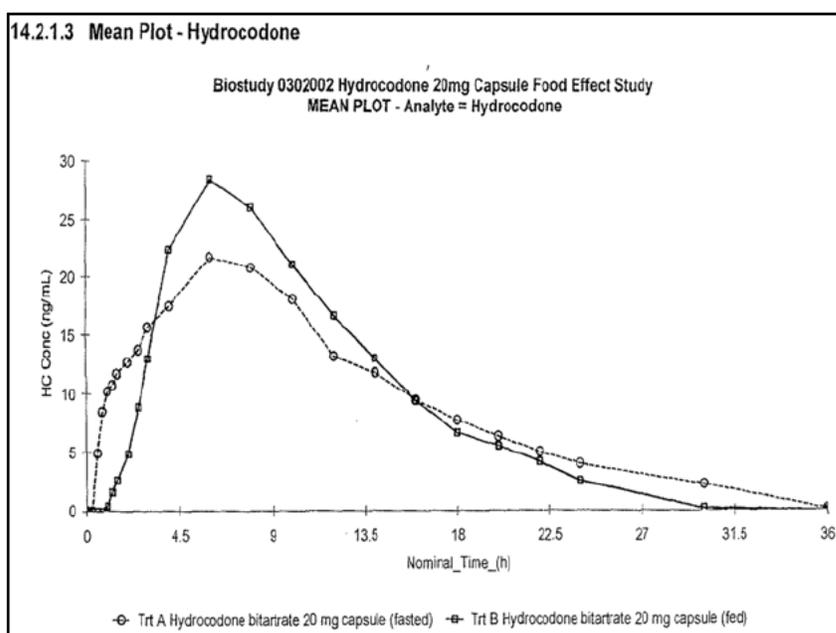
Dose linearity

The Applicant conducted Phase 2 single and multiple-dose studies in bunionectomy and osteoarthritis subjects, respectively. In study ELN154088-201 (bunionectomy patients) linear pharmacokinetics were demonstrated after single doses of 10mg to 40mg. In Study ELN154088-203, multiple-dose PK was obtained on 10, 20, 30, and 40mg BID for 7 days in fed patients. Dose-linear increases in hydrocodone C_{max} and AUC values were observed over the 10mg to 40mg dose range after multiple-dose administration.

Food effect

Food effect was assessed in Study 0302-002. Subjects received a single dose of Zohydro ER following a high fat meal compared with a fasting group of subject. Mean hydrocodone C_{max} values were 28.8 ± 4.2 ng/mL and 22.7 ± 4.3 ng/mL in fed and fasted states, respectively, after a single dose 20 mg Zohydro ER. Mean hydrocodone C_{max} increased approximately 27% in the fed state compared to the fasted state. However, the extent of absorption (AUC) of hydrocodone was similar between fed and fasted (338 ± 55 ng.h/mL vs. 345 ± 37 ng.h/mL, respectively). The hydrocodone median T_{max} were 6 h and 8 h for fasted and fed, respectively. The hydrocodone half-lives were 4.9 ± 1 h and 6.5 ± 0.9 h for fed and fasted states, respectively.

The relative change in C_{max} with food is shown in the graph below from Dr. Lee's review:



Of note, there were two formulations used in clinical studies conducted by the Applicant; the clinical trial formulation (b) (4) % polymer coated spheres produced at Athlone location) and the to-be-marketed formulation (b) (4) % polymer coated spheres produced at Gainesville location). The only trial that used the Athlone formulation was this food effect study. Although the formulation differs from the to-be-marketed formulation in the percentage of polymer coating, the clinical pharmacology review team has recommended that this study be considered adequate and be included in the label based on the following:

1. The formulations produced at the Athlone and Gainesville(to-be-marketed formulation) manufacturing sites are exactly the same, except for the differences in the polymer coating, (b) (4) and (b) (4) %, respectively, and, that the differences are not significant enough to alter the exposure
2. All strengths, 10 to 50 mg, manufactured from the Gainesville manufacturing site were used in clinical studies, including the Phase 3 study, ZX002-0801, such that performance aspects of the formulation are not in question.

3. Comparison of C_{max} across Phase 1 studies indicated, with a caveat that this is a cross-study comparison, that Athlone and Gainsville formulations are not drastically different when ‘fasted’ treatment from the food study is compared to other ‘fasted’ treatments, or ‘fed’ treatment from the food study is compared to other ‘fed’ treatments

Alcohol interaction

Study ZX002-0901 was a Phase 1, open-label, randomized, single-dose, three-period crossover study that assessed the PK of a single dose of 50mg Zohydro ER coingested with orange juice (no alcohol), 20%, and 40% alcohol. Study subjects were appropriately naltrexone blocked.

Mean hydrocodone C_{max} values were 109 ± 39, 52 ± 11, and 46 ± 8.6 ng/mL in 40, 20 and 0% alcohol in the fasted state, respectively. Mean hydrocodone C_{max} increased approximately 2.4-fold in 40% alcohol compared to the 0% alcohol treatments. The greatest increase in C_{max} was observed at 3.9-fold (Subject #016). Mean hydrocodone C_{max} value for 20% alcohol was comparable to 0% alcohol treatment.

Mean hydrocodone AUC values were comparable for all alcohol treatments (1017 ± 217, 900 ± 243, and 846 ± 225 ng.h/mL in 40, 20 and 0% alcohol in fasted state, respectively). Mean hydrocodone AUC was slightly higher for subjects receiving 40% alcohol. The greatest increase in AUC observed was 1.7-fold (Subject #007). This difference was not statistically significant (within bioequivalence range).

Mean hydrocodone T_{max} values were 2.4 ± 1.1, 5.4 ± 1.5, and 6.2 ± 2.1 h in 40, 20 and 0% alcohol in fasted state, respectively. T_{max} decreased to less than half the time for subjects receiving 40% alcohol in comparison to those receiving 20% or 0% alcohol.

This study demonstrated that the rate of absorption (C_{max}) was affected by co-ingestion with 40% alcohol in the fasted state. However, the greatest individual increase in C_{max} was comparable or lower than those of the already approved extended-release opioid products. Therefore, the alcohol interaction with the proposed product is not considered as an approvability issue. Warning language on risks with alcohol consumption will be included in the label.

Hepatic impairment

Study ZX002-1001 was a Phase 1, open-label, single-dose, parallel study in subjects with mild or moderate hepatic impairment who received a single 20mg dose of Zohydro ER in a fasted state, compared with control subjects.

Mean hydrocodone C_{max} values were 25 ± 5, 24 ± 5, and 22 ± 3.3 ng/mL for moderately impaired, mildly impaired and normal subjects, respectively. Mean hydrocodone C_{max} values were comparable for all groups.

Mean hydrocodone AUC values were 509 ± 157, 440 ± 124, and 391 ± 74 ng/mL for moderately impaired, mildly impaired and normal subjects, respectively. Mean hydrocodone AUC increased approximately 26% for moderately impaired subjects compared to that of normal subjects; this increase in exposure may not be clinically significant and may not

warrant a dose adjustment. Severely impaired subjects were not studied. Patients in this population should use a low initial dose and be monitored closely.

Renal impairment

Study ZX002-1002 was a Phase 1, single-dose, parallel study in subjects with mild, moderate, or severe renal impairment per Cockcroft-Gault criteria. Healthy control subjects were matched to renally-impaired subjects. All subjects received a single dose of 20 mg Zohydro ER in a fasted state.

Mean hydrocodone C_{max} values were 26 ± 6.0 , 28 ± 7.5 , 21 ± 5.1 and 19 ± 4.4 ng/mL for severe, moderate, mild renal impaired and normal subjects, respectively. Mean hydrocodone C_{max} values were comparable for all groups.

Mean hydrocodone AUC values were 487 ± 123 , 547 ± 184 , 391 ± 122 and 343 ± 105 ng.h/mL for severe, moderate, mild renal impaired and normal subjects, respectively.

Hydrocodone exposures were similar in moderate or severe renal impairment. However since hydrocodone plasma levels may be increased in patients with moderate to severe renal impairment, patients in this population should receive low initial doses of Zohydro ER and be monitored closely.

Elderly

No formal studies evaluated differences in hydrocodone PK between young and elderly subjects. However elderly subjects are more likely to have compromised renal function and experience higher hydrocodone exposures compared to younger subjects with normal renal function. Therefore, elderly patients should be started on a low dose of Zohydro ER and monitored closely.

Drug interactions

No drug interaction studies were submitted by the Applicant. It is well known that the formation of norhydrocodone is mediated by CYP3A4, while the formation of hydromorphone is primarily mediated by CYP2D6. Inhibition or induction of these enzymes due to interacting drugs or genetic predisposition is likely to alter the metabolic profile of hydrocodone. Therefore, caution is advised when administering Zohydro ER in combination with CYP3A4 inhibitors or inducers. The extent of drug interaction could be more pronounced with concomitant use of CYP 2D6 and 3A4 inhibitors.

Biopharmaceutics

The biopharmaceutics review team was asked to assess this NDA submission for the following:

- Level A IVIVC model
- Dissolution method and acceptance criteria
- Critical process attributes for drug release
- Formulation development
- Dissolution stability

The following are the conclusions and recommendations as stated in Dr. Hughes' review:

CONCLUSION/RECOMMENDATION:

1. DMF (b) (4) was found adequate, with comments, from the Biopharmaceutics perspective to support NDA approval. An adequate response to the DMF comments is pending; however, based on the outstanding issues noted for the DMF, the following conclusions can be made.

- a. The proposed dissolution method and acceptance criteria are acceptable.

Parameter	Criteria
Apparatus	USP 1 (40 mesh baskets)
Paddle Speed	100 rpm
Media	pH 6.8 Phosphate Buffer, 500 mL @ 37°C
Detection	HPLC
Acceptance Criteria	(b) (4)

- b. A Level A IVIVC model submitted under DMF (b) (4) is adequate to support future post-approval drug product changes in accordance with the SUPAC-MR guidance (see DMF review for additional details). The IVIVC model described in the NDA is not the same IVIVC model accepted for regulatory purposes.
2. A biowaiver is granted for the 15 mg capsule strength.
 3. The proposed HC-ER capsule is susceptible to alcohol induced dose dumping in vitro. The safety implication of this finding is assessed by the assigned Clinical Pharmacology and Clinical reviewers.
 4. A major formulation change was noted between product used in a PK food effect study and the product used in the clinical efficacy/safety studies. There were insufficient in vitro dissolution data to bridge the formulation changes; however, the to-be-marketed formulation, including the dose used for the food effect study, was used in the clinical safety and efficacy studies, which included PK assessments. Thus, there may be sufficient in vivo PK data on both formulations to support the adequacy of the food-effect study. The acceptability of the in vivo data is not under Biopharmaceutics purview. Refer to the Clinical Pharmacology review for additional details on the acceptability of the food effect study.
 5. The in vitro and in vivo data support an extended release claim, from the Biopharmaceutics perspective.

4. Clinical Microbiology

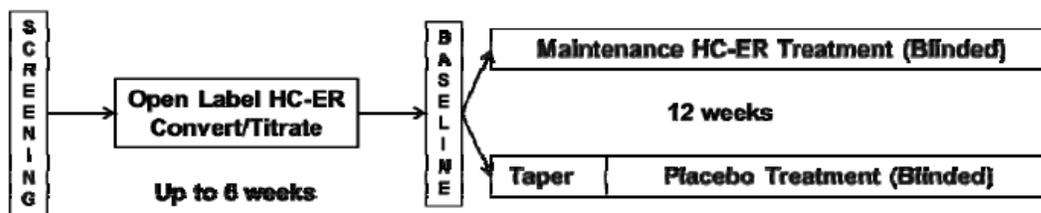
There was no clinical microbiology evaluation of this NDA, as this is not applicable to a solid oral dosage form.

5. Clinical/Statistical- Efficacy

The clinical review of efficacy and safety was performed by Robert A. Levin, MD, and the statistical review by Katherine Meaker, M.S., with secondary concurrence by Dionne Price, Ph.D. Both teams have concluded that the Applicant adequately demonstrated the efficacy of Zohydro ER in the principle efficacy study.

Hydrocodone in combination with non-narcotic analgesics are the most commonly prescribed analgesic in the US, with approximately 131 million prescriptions dispensed in 2011. Because of its wide use for decades as an analgesic, the Agency stated at a Type B meeting with Zogenix in June, 2008, that for a 505(b)(2) application, one principle efficacy study would be sufficient to demonstrate the efficacy of Zohydro ER in an appropriate population for the intended indication. Advice was provided to the Applicant regarding the preferred endpoint (change from baseline in average 24-hour pain intensity), duration of double-blind treatment (12-weeks), and the inclusion of COWS and SOWS assessments to evaluate opioid withdrawal during the trial.

The Applicant conducted and submitted the results of Study ZX002-0801 (henceforth Study 801) with this NDA, a multicenter, randomized double-blind, placebo-controlled trial that used an enriched enrollment randomized withdrawal design to evaluate the efficacy, tolerability and safety of hydrocodone bitartrate extended-release capsules in opioid-experienced subjects with moderate to severe chronic low back pain. The following figure from the Applicant's submission illustrates the design of Study 801.



At screening, subjects were eligible to enter the study if they had a clinical diagnosis of moderate to severe CLBP present for at least several hours a day for a minimum of 3 months; were classified as non-neuropathic (Class 1 and 2), neuropathic (Class 3, 4, 5, and 6), or symptomatic for more than 6 months after low back pain surgery (Class 9) based on the Quebec Task Force Classification of Spinal Disorders; required around-the-clock opioid therapy; were taking opioids for at least 5 days/week for the past 4 weeks at the equivalent of at least an average daily dose of 45 mg oral morphine equivalents per day (as any immediate or ER opioids); had an average clinic pain score ≥ 4 on the 11-point (0-10) Numerical Rating Scale (NRS) for the last 24 hours of the Screening Phase; had stable adjunctive regimens (e.g., physical therapy, biofeedback therapy); were in generally good health; were able to effectively communicate with the study staff and able to complete study procedures; and voluntarily provided written informed consent.

Subjects were excluded from entering the study if they: had any condition that would increase the risk of opioid-related adverse events (e.g., respiratory depression, chronic constipation, and others), had a history of illicit substance or alcohol abuse in the past 5 years or any history of opioid abuse, positive urine drug screen for illicit drugs or non prescribed controlled substances, had severe depression or anxiety, active fibromyalgia or other pain syndrome, spinal or back pathology, condition that would interfere with the assessment of low back pain, were obese, or had allergy to any of the study drugs.

During the open-label conversion/titration phase, subjects were converted to a dosage of Zohydro ER that was approximately 20%-30% less than the conversion dose of Zohydro ER calculated based on their prior opioid treatment, using a conversion table based on approximate equivalent doses of other opioids to hydrocodone. Subject was titrated if needed, in an open-label fashion to achieve adequate analgesia. Rescue medication consisted of up to 4 tablets per day of immediate-release hydrocodone 5mg/APAP 500mg. A stabilized dose was one that subjects tolerated well for at least 7 days with an average 24-hour daily average pain score of ≤ 4 on the NRS during the last 7 days prior to Baseline, a reduction of 2 points on the NRS compared to Screening, and no more than 2 tablets of rescue medication on any day. Subjects who did not achieve a stabilized dose, who did not tolerate Zohydro ER treatment due to AEs, who were not compliant with dosing or drug accountability, or who could not complete required study procedures (e.g. study visits, use of the electronic diary) were discontinued from the study.

Subjects were randomized 1:1 to receive either Zohydro ER or placebo if they met the above criteria and had been stabilized on 40 to 200mg per day. The dosage could not be adjusted during the 12-week maintenance period. The initial 14-day supply of study medication contained a tapering dose of Zohydro ER for subjects randomized to placebo, and a mock taper for those randomized to Zohydro ER. Allowed rescue medication was hydrocodone 5mg/APAP 500mg up to two tablets per day. All other opioids, analgesics and other possibly confounding medication were prohibited during the study.

The primary efficacy endpoint of the study was the change from Baseline (randomization) to the end of the double-blind maintenance treatment phase (Day 85 or last visit) in average pain intensity on the 11-point NRS as recorded daily in an electronic diary, comparing Zohydro ER with placebo. Secondary efficacy endpoints included the response rate (with response defined as a 30% improvement from the screening pain intensity score to the Day 85 pain intensity score) and the Subject Global Assessment of Medication, SGAM. Although not specified in the protocol or subsequent protocol amendments, the Statistical Analysis Plan incorporated a hierarchical testing procedure for these endpoints.

Study 801 Results

Of the total 510 subjects enrolled, 302 subjects (59%) completed the conversion/titration (C/T) phase and were randomized to treatment and 208 subjects (41%) discontinued the C/T phase early. Of the 302 subjects randomized, 151 subjects (30%) were randomized to receive Zohydro ER and 151 subjects (30%) were randomized to receive placebo. Forty-one percent of subjects discontinued early from the C/T phase. The most common reasons included protocol violation, noncompliance with study drug, adverse events, and lack of efficacy.

One hundred eighty-three subjects completed the treatment phase, 124 received Zohydro ER and 59 placebo. The most common reasons for discontinuation during this phase in the Zohydro ER group were lack of efficacy (9%), noncompliance with study drug (3%), and adverse event (1%). As would be expected the most common reason for withdrawal from the placebo group was lack of efficacy (42%), followed by noncompliance with study drug (5%) and adverse event related to opioid withdrawal (5%). The large proportion of dropouts from the placebo group was likely due to the small amount of rescue medication allowed during this phase of the trial (a maximum of 2 hydrocodone 5mg/APAP 500mg tablets per day).

In terms of demographics the mean age was approximately 50 years, the percentage of females in the study was slightly greater than males (C/T phase 55% ; Treatment phase: 61% Zohydro ER, 49% placebo), and the majority of subjects were white (77-82% depending on phase and treatment). The average pain score at screening was approximately 7/10 on an 11-point NRS for all phases, and baseline average pain score (at beginning of treatment phase) was approximately 3/10.

The primary efficacy endpoint for Study 801 was the mean change from Baseline to Day 85 in the Treatment Phase in the average 24-hour pain intensity scores on a 0-10 NRS based on subject diaries. Baseline was defined as the mean of the last 7 days on stabilized dosing of the average pain intensity rating prior to randomization into the maintenance treatment phase. Day 85 was defined as the mean of the last 7 days of the average pain intensity rating prior to Day 85 study visit of the treatment phase.

The primary efficacy analysis population was the Intent-To-Treat (ITT Population), and all 302 randomized subjects were included in the analysis. Missing pain scores were imputed using methods agreed upon between the Applicant and the Agency at the EOP2 meeting: baseline observation carried forward for subjects who discontinued due to opioid withdrawal; screening observation carried forward for subjects who discontinued due to AEs; and last observation carried forward for subjects who discontinued due to lack of efficacy and other reasons.

The primary efficacy analysis used an analysis of covariance (ANCOVA) model. The dependent variable was the change from baseline to Day 85. The model included treatment group as a factor and the baseline pain score and screening pain score as covariates. The Zohydro ER and placebo groups were compared at the 5% level of significance. The table below from the Applicant's submission shows the results of the primary endpoint analysis.

Table 15: Primary Efficacy Endpoint: Change from Baseline of Average Daily Pain Intensity Score (patient diary), ITT population, Study 801

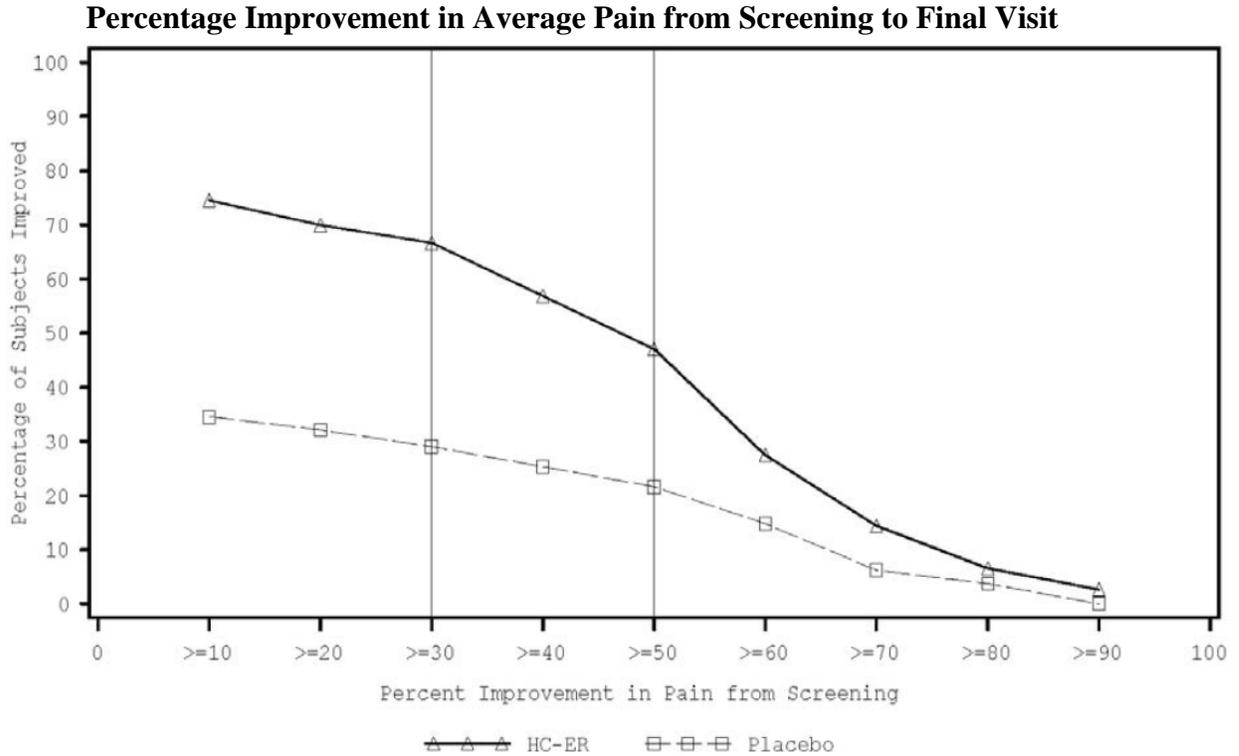
Change from Baseline	HC-ER (N=151)	Placebo (N=151)
Mean (SD)	0.48 (1.563)	0.96 (1.550)
Range	-3.0 – 5.3	-2.4 – 6.7
LS Mean	0.48	0.95
p-value ^a		0.008

^a Treatment comparison using ANCOVA with treatment group as a fixed effect and screening pain score and baseline pain score as covariates.
ANCOVA = analysis of covariance.

Zohydro ER was superior to placebo in the change from Baseline to the end of study in average daily pain intensity score (p=0.008). The statistical review team was able to replicate the Applicant's analysis of the primary endpoint.

A continuous responder graph was also provided. The graph depicted the percentage of subjects achieving improvement across all possible cut-offs. All patients who discontinued were defined as non-responders. As shown in the figure below from the Applicant's

submission, a greater percentage of subjects in the Zohydro ER group compared to placebo group showed improvement in pain across all response rates



Other secondary endpoints that supported the primary analysis included the Subject Global Assessment of Medication, Worst Pain Intensity, Least Pain Intensity, and Time to Treatment Discontinuation. Analyses of these endpoints were numerically in favor of Zohydro ER.

The results of the analysis of rescue medication use during the double-blind treatment phase were somewhat atypical. Rescue medication during this phase was limited to 2 tablets per day of hydrocodone 5mg/APAP 500mg. The mean total daily dose of rescue for the hydrocodone component only in the Zohydro ER group was 6.0mg mg \pm 3.4 mg, with a range from 0.1 mg to 12.5 mg. In the placebo group, the mean TDD of rescue medication was 7.5 mg \pm 3.9 mg, with a range from 0.1 mg to 20 mg. The most likely explanation for the small difference between treatment groups in the use of rescue is the relatively low limit on the amount of allowed rescue medication.

I am in agreement with Dr. Levin that the Applicant adequately demonstrated efficacy for Zohydro ER in the selected chronic pain population.

6. Safety

Dr. Robert A. Levin conducted the safety review for this NDA, and I concur with his findings.

The Zohydro ER clinical development program consisted of 10 clinical studies: six phase I studies, two phase 2 studies and two phase 3 studies. The Applicant has provided adequate

exposure to assess safety, with a total of 1512 subjects exposed to at least one dose of Zohydro ER, 332 subjects exposed for at least 6 months, and 290 subjects for at least one year. For Study 801, the maximum dose was 200mg/day, however in the open-label study 802, the maximum dose was up to 600mg/day.

There were five deaths among the 575 subjects in the chronic pain population exposed to Zohydro ER. Four deaths occurred during Study 802 as follows: completed suicide (carbon monoxide poisoning), drug toxicity (methadone and oxycodone), lung cancer, and coronary artery disease. The fifth death was an apparent suicide from an overdose of Zohydro ER approximately a year after the end of the study, in a patient who hoarded study medication during Study 802. Dr. Levin reviewed the deaths and concluded that the first four were unlikely related to study medication, and the fifth, while related, occurred a year after the study was completed.

Eighty-one subjects exposed to Zohydro ER reported a total of 118 nonfatal serious adverse events (SAEs). During the C/T phase, 22 subjects reported 32 nonfatal SAEs, and during the treatment phase, 56 subjects reported 83. There were no SAEs reported in the 151 subjects taking placebo, however, most of the SAEs occurred in Study 802 where there was no placebo group. The following table from Dr. Levin's review shows the SAEs observed in more than one subject in the chronic population:

Table 1: Medical Serious Adverse Events Observed in More than One Subject Chronic Population, Treatment Phase

Preferred term ^a	HC-ER			ZX002-0801
	ZX002-0801 N=151	ZX002-0802 N=424	Total N=575	Placebo N=151
Subjects with at least 1 medical SAE	5 (3.3%)	52 (12.0%)	56 (9.7%)	
Chronic obstructive pulmonary disease	0	5 (1.2%)	5 (0.9%)	0
Osteoarthritis	0	4 (0.9%)	4 (0.7%)	0
Pneumonia	0	3 (0.7%)	3 (0.5%)	0
Dehydration	0	2 (0.5%)	2 (0.3%)	0
Small intestinal obstruction	0	2 (0.5%)	2 (0.3%)	0
Intentional overdose	0	2 (0.5%)	2 (0.3%)	0
Hypokalaemia	1 (0.7%)	1 (0.2%)	2 (0.3%)	0
Anaemia	1 (0.7%)	1 (0.2%)	2 (0.3%)	0
Non-cardiac chest pain	1 (0.7%)	1 (0.2%)	2 (0.3%)	0
Depression	1 (0.7%)	1 (0.2%)	2 (0.3%)	0

Percentages are based on the number of subjects in each column.

Subjects were counted once within each preferred term.

^aAll investigator adverse event terms were coded using MedDRA dictionary version 12.1.

Source: ISS (June 14, 2012), p.133

Dr. Levin reviewed the patient narratives for all SAEs. The SAEs he determined to be reasonably related to Zohydro ER are consistent with the known safety profile of extended-release opioids, and include the following: anxiety (1), mental impairment (2), small bowel obstruction (2) and abdominal distension/constipation (3). Dr. Levin reviewed three events coded as SAE due to an overdose and determined that these cases were neither overdoses nor

SAEs. The protocol of the study (Study ELN-154088-203) from which these cases were reported defined an overdose as taking more pills than prescribed whether or not there were any clinical sequelae. Each of these cases took one extra dose of study drug because they forgot whether they had taken their previous dose, and none experienced any adverse event related to the extra dose.

Dr. Levin also reviewed all narratives for subjects discontinuing treatment due to adverse events. The most common adverse events leading to study discontinuation were not unexpected for an opioid and included nausea, somnolence, headache, constipation, vomiting, lethargy, fatigue, and cognitive changes. The following two tables from Dr. Levin's review summarize discontinuation due to adverse events in the C/T Phase and the Treatment Phase of Studies 801 and 802.

Table 2: Adverse Events that Led to Discontinuation of More Than One Subject in the Chronic Population, C/T Phase

Preferred term ^a	HC-ER		
	ZX002-0801 N=510	ZX002-0802 N=638	Total N=1148
Subjects with at least 1 TEAE that led to discontinuation	55 (10.8%)	66 (10.3%)	121 (10.5%)
Nausea	15 (2.9%)	10 (1.6%)	25 (2.2%)
Somnolence	4 (0.8%)	9 (1.4%)	13 (1.1%)
Headache	3 (0.6%)	7 (1.1%)	10 (0.9%)
Constipation	7 (1.4%)	3 (0.5%)	10 (0.9%)
Vomiting	6 (1.2%)	4 (0.6%)	10 (0.9%)
Lethargy	2 (0.4%)	7 (1.1%)	9 (0.8%)
Insomnia	2 (0.4%)	7 (1.1%)	9 (0.8%)
Dizziness	2 (0.4%)	2 (0.3%)	4 (0.3%)
Oedema peripheral	1 (0.2%)	3 (0.5%)	4 (0.3%)
Pruritus allergic	2 (0.4%)	2 (0.3%)	4 (0.3%)
Fatigue	3 (0.6%)	0	3 (0.3%)
Abdominal pain	2 (0.4%)	1 (0.2%)	3 (0.3%)
Agitation	2 (0.4%)	0	2 (0.2%)
Depression	2 (0.4%)	0	2 (0.2%)
Anxiety	1 (0.2%)	1 (0.2%)	2 (0.2%)
Non-cardiac chest pain	1 (0.2%)	1 (0.2%)	2 (0.2%)
Pain in extremity	1 (0.2%)	1 (0.2%)	2 (0.2%)
Haematochezia	1 (0.2%)	1 (0.2%)	2 (0.2%)
Hyperhidrosis	1 (0.2%)	1 (0.2%)	2 (0.2%)
Drug withdrawal syndrome	0	2 (0.3%)	2 (0.2%)
Feeling jittery	0	2 (0.3%)	2 (0.2%)
Irritability	0	2 (0.3%)	2 (0.2%)
Arthralgia	0	2 (0.3%)	2 (0.2%)

Percentages are based on the number of subjects in each column.

Subjects were counted once within each preferred term.

All investigator adverse event terms were coded using MedDRA dictionary version 12.1.

Drug diversion events are not included in this table.

Source: ISS (June 14, 2012), p.137

Table 3: Adverse events that Led to Discontinuation of More than One Subject in the Chronic Population, Treatment Phase

	HC-ER			ZX002-0801 Placebo N=151
	ZX002-0801 N=151	ZX002-0802 N=424	Total N=575	
Preferred term^a				
Subjects with at least 1 TEAE that led to discontinuation	3 (2.0%)	34 (8.0%)	37 (6.4%)	16 (10.6%)
Abdominal pain upper	0	2 (0.5%)	2 (0.3%)	0
Constipation	0	2 (0.5%)	2 (0.3%)	0
Cognitive disorder	0	2 (0.5%)	2 (0.3%)	0
Back pain	1 (0.7%)	1 (0.2%)	2 (0.3%)	2 (1.3%)
Withdrawal syndrome	1 (0.7%)	0	1 (0.2%)	6 (4.0%)
Insomnia	0	1 (0.2%)	1 (0.2%)	2 (1.3%)

Percentages are based on the number of subjects in each column.

Subjects were counted once within each preferred term.

All investigator adverse event terms were coded using MedDRA dictionary version 12.1.

Drug diversion events are not included in this table.

Source: ISS (June 14, 2012), p.138

Common adverse events noted in Studies 801 and 802 were consistent with the opioid class of drugs and include constipation, nausea, somnolence, fatigue, headache, and dizziness. The following table from Dr. Levin's review shows adverse events occurring in at least 2% of subjects in Study 801.

Table 4: Adverse Events in ≥2% of Subjects in ZX002-0801

	Open-Label Titration Period	Double-Blind Treatment Period	
	Zohydro (N = 510)	Zohydro (n = 151)	Placebo (n = 151)
Constipation	56 (11.0%)	12 (7.9%)	0 (0.0%)
Nausea	50 (9.8%)	11 (7.3%)	5 (3.3%)
Somnolence	24 (4.7%)	1 (0.7%)	0 (0.0%)
Fatigue	21 (4.1%)	1 (0.7%)	2 (1.3%)
Headache	19 (3.7%)	0 (0.0%)	2 (0.7%)
Dizziness	17 (3.3%)	3 (2.0%)	1 (0.7%)
Dry Mouth	16 (3.1%)	0 (0.0%)	0 (0.0%)
Vomiting	14 (2.7%)	7 (4.6%)	1 (0.7%)
Pruritus	13 (2.5%)	0 (0.0%)	0 (0.0%)
Abdominal Pain	8 (1.6%)	4 (2.6%)	0 (0%)
Edema peripheral	7 (1.4%)	4 (2.6%)	0 (0.0%)
Upper respiratory tract infection	7 (1.4%)	5 (3.3%)	1 (0.7%)

	Open-Label Titration Period	Double-Blind Treatment Period	
	Zohydro	Zohydro	Placebo
Preferred Term	(N = 510)	(n = 151)	(n = 151)
Muscle spasms	6 (1.2%)	4 (2.6%)	2 (1.3%)
Urinary Tract Infection	4 (0.8%)	8 (5.3%)	3 (2.0%)
Back Pain	4 (0.8%)	6 (4.0%)	5 (3.3%)
Tremor	1 (0.2%)	4 (2.6%)	1 (0.7%)

Source: Tables 14.3.9.3.1 and 14.3.9.3.2 in the ISS (June 14, 2012)

In the long-term open-label safety study (ZX002-0802), the common adverse events were reviewed by Dr. Levin and found to be similar to Study 801. The most common adverse events during the C/T Phase Study 802 were: constipation (11.3%), nausea (10.7%), somnolence (7.7%), headache (7.5%), vomiting (4.1%), insomnia (3.8%), fatigue (3.6%), diarrhea (3.1%), dizziness (2.8%), dry mouth (1.9%) and pruritus (1.7%). In the treatment phase the most common adverse events were: constipation (12.5%), back pain (11.1%), nausea (9.9%), vomiting (9.7%), arthralgia (7.8%), headache (6.8%), urinary tract infection (6.6%), upper respiratory tract infection (5.9%), fall (5.9%), anxiety (5.4%), nasopharyngitis (5.7%), sinusitis (5.4%), insomnia (5.0%). Additional adverse events reported that are often associated with opioids included somnolence (4.2%), fatigue (3.5%), confusion (3.3%), and dizziness (3.1%).

There were no clinically meaningful changes in laboratory assessments (hematology and clinical chemistry) in the chronically treated subjects in Studies 801 and 802. Vital signs were monitored at each study visit in the two chronic studies, and no clinically significant unexpected changes in any of the parameters monitored (blood pressure, pulse, temperature, respiratory rate) were observed. Mild changes in blood pressure were consistent with the hypotensive effect known to occur with opioids.

In Study ELN-154088-201, the single-dose post-bunionectomy study, hypoxia was reported as an adverse event in four subjects and oxygen desaturation was reported in an additional three subjects. The oxygen saturation values for the four subjects reported to have hypoxia were all greater than 90%. Two of the subjects were on Zohydro ER (10 mg and 30 mg), one subject was on 10 mg HC/APAP and one subject was on placebo. There were three subjects with oxygen saturation below 90% (87%, 89% and 89%). Two subjects were on Zohydro ER (10 mg and 20 mg) and one subject on 10 mg HC/APAP. There did not appear to be a dose response with Zohydro ER and hypoxia or desaturation (i.e., no case on the highest dose 40 mg and only one case on the next highest dose, 30 mg). This finding of oxygen desaturation during the post-operative period is not unexpected. The label specifically notes that Zohydro ER is not indicated in the immediate postoperative period.

ECGs were collected at screening and end of study in 159 subjects in four Phase 1 and 2 studies. Data for P-R interval, QRS interval, and QT interval were reviewed and no meaningful changes were identified in these parameters. Interpretation of the findings is

limited because ECGs were not collected at Cmax, and the highest dose administered was 40mg.

Special Safety Issue-audiology assessments

Since progressive hearing loss has been associated with the abuse of hydrocodone/acetaminophen combination products, and the potential exposure to hydrocodone from this Zohydro ER is higher than the labeled doses from combination products, the Division requested that Zogenix perform audiometry assessments to monitor for potential hearing loss in the principle clinical efficacy trial. Results of the audiometry evaluations performed on 510 subjects in Study 801 were reviewed by James Kane, Ph.D. from the Center for Devices and Radiological Health (CDRH) at the FDA. He concluded that Zohydro ER appears not to affect hearing sensitivity for the dosages studied (maximum Zohydro ER dose allowed in Study ZX002-0801 was 200 mg per day). Details regarding his consult response may be found in Dr. Levin's review.

Misuse, Abuse, and Diversion

The Controlled Substance Staff was consulted to review data regarding misuse, abuse, and diversion of Zohydro ER during the clinical trials; however they have not yet completed their review. The Applicant utilized "diversion events" reported during the Phase 3 trials as a measure of abuse-related events. The Applicant included cases where missing drug was observed, and the study medication could not be 100% accounted for at either the site or subject level. The cases were classified under a number of categories including "administrative serious adverse events". For those considered administrative in nature, the Applicant did not supply narratives, but did provide adverse event report forms.

The Applicant reported 92 diversion-related adverse events in studies 801 and 802. Sixty three possible cases of drug diversion were identified in studies 801 and 802, 13 in Study 801 (2.5%), and 50 in Study 802(7.8%), and six cases of possible abuse. Examples of abuse included tampering with the urine drug screen sample, and tampering with the rescue medication to extract hydrocodone, and obtaining prescriptions from more than one prescriber for hydrocodone/acetaminophen.

As a Schedule II opioid analgesic, it is not unexpected that events of misuse, abuse, and diversion would be reported during the clinical trials of Zohydro ER. Hydrocodone is a Schedule II opioid analgesic with abuse liability similar to other drugs its class. In fact, additional in vivo human abuse liability studies were not required for this application since the abuse liability of this drug substance is well known, and the Applicant has made no claims that Zohydro ER is an abuse deterrent formulation.

Safety Summary

In summary, the safety data provided by the Applicant has demonstrated that during the development of Zohydro ER, the safety profile is consistent with other extended-release opioid analgesics when used as labeled in patients with chronic pain who require treatment with an around-the-clock opioid analgesic. While there were reports of diversion and abuse during the clinical trials, this is not unexpected for a drug in this class. No new or unexpected safety signals were identified during review of this NDA.

7. Advisory Committee Meeting

The Anesthetic and Analgesic Drug Products Advisory Committee met on December 7, 2012 to discuss this NDA. Although the Division was in agreement with the Applicant that they had provided sufficient evidence that their product is safe and effective when used according to the product labeling and inclusion of Zohydro in the ER/LA REMS, it was determined that it was important to present this application to the advisory committee to obtain their input on the product's potential for abuse and misuse, how this may compare to the already approved products in the ER/LA class, and whether these issues should affect the approvability of Zohydro.

The committee was reminded during Dr. Rappaport's introductory comments that if approved, Zohydro ER will be the first FDA approved and marketed, single-entity hydrocodone analgesic product, and will be available in an extended-release formulation. While combination hydrocodone products are currently controlled under CSA Schedule III, this new single-entity product would be controlled under Schedule II, as are the other single entity ER/LA opioids. In addition, Zohydro ER as a member of the ER/LA opioid class would fall under the ER/LA REMS that was approved in July, 2012. Dr. Rappaport stated that regardless of the existing REMS, it can be anticipated that a single-entity hydrocodone product will contribute to the already critical public health problem of prescription opioid abuse and misuse. And, it is also important to recognize that this product may be a useful addition to the armamentarium of analgesic drug products that treat chronic pain.

The Agency's presentations during the AC meeting included drug utilization for the combination hydrocodone products by the Office of Safety and Epidemiology (OSE), that stated that the utilization of combination hydrocodone containing analgesics far exceeded all other opioid analgesics analyzed; the Division of Epidemiology within OSE, that discussed the potential risk of abuse of a single entity ER hydrocodone product based on the experience with combination IR oxycodone products and single-entity ER oxycodone. The findings showed that the abuse ratio (ER visits/number of tablets dispensed) of single-ingredient ER oxycodone products is 3-4 fold higher than combination IR oxycodone products (although there are limitations to this analysis as the numerator and denominator data are not linked), which may be predictive of the pattern expected with hydrocodone; and a presentation by Dr. Sharon Walsh who discussed abuse liability studies of hydrocodone conducted in healthy volunteers and opioid abusers that showed the profile for hydrocodone is similar to comparator opioids, including morphine, hydromorphone and oxycodone.

The Applicant presented a summary of their proposed additional risk management tools that they intend to utilize to supplement the ER/LA opioid analgesic REMS. The proposal includes:

1. Commercialize Zohydro ER responsibly (prescriber target audience, pain docs, pain journals, incentivize education,)
2. Augment the ER/LA REMS with their voluntary Zohydro ER Safe-Use initiative that is designed to
 - i. Increase and improve participation in training programs and monitor effectiveness
 - ii. Uphold safe use among patients

- iii. Implement rigorous utilization surveillance systems
- iv. Take corrective actions if issues are detected

The following is a brief summary of the questions asked of the advisory committee and their votes and discussion.

1. **VOTE: Has the Applicant demonstrated that Zohydro ER is effective for the management of moderate to severe chronic pain when a continuous around-the-clock opioid analgesic is needed for an extended period of time?**

Vote: *Yes = 7* *No = 6* *Abstain = 1*

Discussion

The committee members who voted “Yes” stated that the Applicant had met the efficacy standards set forth by the Agency, and they agreed that the data suggest that Zohydro ER is efficacious, especially given the history of efficacy of combination hydrocodone/acetaminophen products. The committee members who voted “No” and the member who abstained agreed that the length of the 12- week study period was not sufficient to demonstrate efficacy for a chronic use indication

2. **VOTE: Has the Applicant demonstrated that Zohydro ER is safe in the intended population?**

3. *Vote:* *Yes = 5* *No = 9* *Abstain = 0*

Discussion

The committee agreed that the Applicant met the safety standards set forth by the Agency and stated that Zohydro ER is as safe as other long-acting and extended-release opioid analgesics that have previously been approved. However, the majority of the committee did not agree that the Applicant demonstrated that Zohydro ER is safe in the intended population. The committee members who voted “No” shared their concerns about long-term safety risks including risk of addiction. Additionally, these committee members noted that drug diversion and deaths still occurred in clinical trials despite close monitoring, and that frequency of these adverse outcomes would likely be worse in real life clinical practice in the absence of close monitoring.

4. **DISCUSSION: Please discuss whether the data presented or discussed suggest that the postmarketing experience concerning abuse with Zohydro ER would be expected to be different from the postmarketing experience associated with other approved Schedule II extended-release opioids.**

Discussion

Some committee members thought that the post-marketing experience concerning abuse would be similar to other ER/LA opioids while others thought that Zohydro ER would be abused more than members of the class. There was concern that since the combination hydrocodone/acetaminophen products are the most widely abused opioid, Zohydro ER would be more likely to be abused due to the absence of acetaminophen.

5. DISCUSSION: Please discuss whether the data support the need for additional postmarketing risk mitigation requirements beyond the ER/LA REMS.

Discussion

The committee felt that the current ER/LA Opioid Analgesic REMS will at best be modestly effective in addressing the public health issues of opioid abuse and misuse for ER/LA opioids in general, including Zohydro ER. They stated there is a need for additional postmarketing risk mitigation requirements beyond the current REMS for the entire class.

6. VOTE: Based on the data presented and discussed today, do the efficacy, safety and risk-benefit profile of Zohydro ER support the approval of this application?

Vote: Yes= 2 No = 11 Abstain = 1

Discussion:

The committee agreed that standards for opioid product approval should be raised in light of the current public health concerns of abuse and misuse. The committee stated that the FDA should not approve ER/LA opioid analgesics without tamper/abuse-deterrent properties, and that additional risk mitigation features should be adopted to strengthen the current ER/LA Opioid Analgesic REMS.

8. Pediatrics

The Division's current policy for pediatric studies for extended-release opioid analgesics under PREA is to waive studies in patients less than 7 years old because there are too few patients with chronic pain in this age group to study. Based on the Division's 2009 workshop that included thought leaders in pediatric analgesic clinical trials and treatment of pediatric pain, the determination was made that the efficacy of certain classes of drugs, including opioids, could be extrapolated from adults to pediatric patients ages 2 years and older. The reason for extrapolation is based on the fact that the exposure response to opioids and mechanism of underlying pain is expected to be similar in children and adults.

The Applicant's initial Pediatric Plan submitted with the NDA was not in line with the above requirements. The Applicant submitted a revised pediatric plan as follows, which appears acceptable. This plan was presented to the Pediatric Research Committee on January 30, 2012, and they concurred with the plan.

The Applicant has requested a waiver for studies in patients less than 7 years of age, and deferral of PK and safety studies in patients 7 to <12 years and 12 to < 17 years. They propose to conduct two separate open-label PK and safety studies with Zohydro ER in opioid-experienced pediatric subjects with chronic pain. The first study will enroll subjects aged 12 to < 17 years of age, and the second study will enroll subjects ages 7 to < 12 years.

The Applicant anticipates that some subjects may require doses lower than the current lowest developed dosage strength of Zohydro ER (10 mg). While the six (10, 15, 20, 30, 40, and 50 mg) current dosage strengths of Zohydro ER represent (b) (4)

(b) (4) cannot be produced using the current manufacturing process (b) (4) The Applicant proposes to develop (b) (4)

The proposed timeline for the studies is:

Pediatric Subjects Ages 12 to <17

- Protocol submitted for review – 12 months from NDA approval
- Study start – 24 months from NDA approval
- Study stop – 66 months from NDA approval
- Final report submitted – 72 months from NDA approval

Pediatric Subjects Ages 7 to <12

- Protocol submitted for review – 48 months from NDA approval
- Study start – 60 months from NDA approval
- Study stop – 96 months from NDA approval
- Final report submitted – 102 months from NDA approval

9. Other Relevant Regulatory Issues

Financial disclosure

The Applicant adequately disclosed financial arrangements with clinical investigators, and has submitted Debarment Certification and FDA form 3454 certifying that the clinical investigators who supervised studies in support of this application:

- Did not participate in any financial arrangement with the sponsor, whereby the value of compensation to the investigators for conducting the study could be affected by the outcome of the study [as defined in 21 CFR 54.2(a)];
- Had no proprietary interest in this product or significant equity interest in the sponsor [as defined in 21 CFR 54.2(b)]; and
- Was not the recipient of significant payments of other sorts [as defined in 21 CFR 54.2(f)]

Office of Scientific Investigation (OSI) audit

The Division consulted OSI to conduct a routine audit for the principle efficacy study, 801, which was a multicenter study and included 57 U.S. sites. The two sites with the highest enrollment were chosen for inspection. The sites inspected were Dr. George Walker, site 136, and Dr. Raymond Tidman, site 112.

As per the OSI review dated January 13, 2013, neither site was issued a Form FDA 483; the preliminary classifications of both inspections were NAI (No Action Indicated). In general, based on the inspection of the two clinical study sites, the inspectional findings support validity of data as reported by the sponsor under this NDA.

Controlled Substance Staff (CSS)

The Division consulted CSS to provide input regarding the abuse potential of Zohydro ER based on review of the NDA submission. The Applicant did not conduct any human abuse

liability studies, however did collect information in clinical studies regarding abuse, misuse and diversion of Zohydro ER. At the time of this writing, the review has not been completed or filed into DARRTS. Findings from the CSS review will be reflected in the decisional memo for this NDA.

10. Labeling

The Zohydro ER label is currently under review. The extended-release opioid class Medication Guide is required for Zohydro ER, and is being reviewed by the Patient Labeling Team. The following consulting divisions have completed their reviews and provided guidance regarding labeling.

The Division of Medical Error Prevention and Analysis (DMEPA) conducted a review of the label, labeling and packaging dated October 3, 2012. Recommendations were provided to improve the clarity of the label and packaging to reduce the chance of medical errors, and these were conveyed to the Applicant and implemented.

DMEPA also reviewed the proprietary name proposed by the Applicant. The proposal initially was Zohydro. This was deemed unacceptable because of a lack of modifier, and since there were overlapping strengths with the marketed IR combination hydrocodone products, a modifier was requested. On June 14, 2012, the Applicant submitted the name Zohydro ER for review, which was determined to be acceptable from both a promotional and safety perspective. See the DMEPA review dated September 12, 2012 for additional details.

The OPDP and patient labeling team reviews of the label and Medication Guide are pending at this writing.

11. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval

- Risk Benefit Assessment

The Applicant has demonstrated the efficacy of Zohydro ER, as required by the Agency, in a single adequate and well-controlled clinical trial in subjects with chronic low back pain, and has shown that the safety profile appears similar to other approved extended-release opioid analgesics. There were no unexpected or unusual safety signals that were reported during Zohydro ER's clinical development. Although there were reports of abuse and diversion during the clinical studies, this is not unexpected for a drug in this class. And like other drugs in this class, the ER/LA REMS is required in order to ensure safe use and mitigate problems regarding misuse and abuse. It would seem that there are no issues that would preclude approval of Zohydro ER for the proposed indication, the management of moderate to severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time; however, as noted in Section 7 of this review, the Anesthetic and Analgesic

Drug Product Advisory Committee voted 11 to 2 against the approval of this NDA, citing the lack of a tamper/abuse deterrent formulation of Zohydro ER, and the need to strengthen the current ER/LA REMS with additional risk mitigation components, not just for Zohydro ER but for all drugs in the ER/LA opioid analgesic class. The committee also stated that the Agency should not approve any extended-release opioid analgesics that do not have abuse deterrent or tamper resistant properties.

Although we are strongly encouraging sponsors to develop opioid analgesics that have abuse/tamper resistant properties as one of the ways the Agency can address the public health epidemic of increased prescription opioid abuse, there are currently no regulations or policies within the Agency that state that a drug in this class must have abuse deterrent characteristics. Additionally, while there is pressure from the public and the advisory committee not to approve this drug because it will likely be abused to a great extent, there is also another important public health issue that must be taken into consideration, the widespread inadequate treatment of pain. The approval of a single-entity extended-release hydrocodone product will add to the armamentarium to treat chronic pain, and allow for another option for patients and prescribers when rotating opioids due to the development of tolerance. Hydrocodone will be available as a single-entity product and will therefore be titratable to an effective dose without concern regarding the toxicity of acetaminophen present in the currently available combination products. Finally, twice daily dosing will provide convenience to patients who currently use the IR combination 4 times per day for chronic pain.

A Center Director Briefing is scheduled for February 6, 2013, in order to obtain input regarding the approvability of this application. Regulatory options for this application will be discussed, and include non approval (either because it is not an abuse deterrent formulation or because the ER/LA REMS requires additional risk mitigation components), approving all doses for the proposed indication, limiting the approval to the lower dosage strengths until postmarketing safety information is available on those strengths and then consider approval of higher strengths, and limiting the approval to 12-weeks duration of treatment based on the length of the clinical trial.

Non approval of this application based on Zohydro ER's lack of abuse deterrent properties does not appear to be a viable regulatory option, since there is currently no regulation or policy that mandates that ER/LA opioid analgesics have these properties. Non approval because the ER/LA REMS requires strengthening is also problematic, as the purpose of strengthening the ER/LA REMS would be to mitigate risks of all drugs in this class, not just Zohydro ER, and this process would require significant Agency time and resources that are beyond the scope of this NDA.

It is my opinion that approving only the lower dosage strengths of Zohydro ER does not solve issues regarding abuse, misuse and diversion. The drug product would still be available, and patients would likely have a larger pill burden to obtain the dosage needed to alleviate their pain. The larger number of pills available would increase opportunity for diversion. Also, ER/LA opioids are approved and marketed at dosages that are more potent than the highest dosage unit of Zohydro ER.

Approving Zohydro ER for only 12-weeks duration of treatment based on the duration of the clinical trial would be unlikely to affect abuse or misuse, and no other drug in this class has labeling limiting the duration of treatment, despite clinical trials of similar durations. In addition, there are patients with chronic pain who may benefit from treatment beyond 12 weeks.

Therefore, although I have concerns regarding the abuse and misuse of Zohydro ER, these concerns are similar for all of the marketed, non-abuse deterrent formulations of ER/LA opioid analgesics. Until the Agency develops a regulation or policy that requires this class of drug have abuse deterrent or tamper resistant properties, the only viable regulatory option at this time is to approve Zohydro ER for the proposed indication.

As the Center Director Briefing is being held after this review is complete, input from the Center Director will be reflected in the Decisional Memo for this NDA.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

As a member of the extended-release class of opioid analgesics, the ER/LA opioid analgesic REMS is required for its approval. The ER/LA REMS will be modified appropriately to include Zohydro ER and any drug specific information that may be needed.

- Recommendation for other Postmarketing Requirements and Commitments

Pediatric trials required under PREA

- Safety and pharmacokinetic study in pediatric patients ages 7 to <12 years with chronic pain requiring around-the-clock treatment with an opioid
- Safety and pharmacokinetic study in pediatric patients ages 12 to <17 years with chronic pain requiring around-the-clock treatment with an opioid

Nonclinical studies

- Fourth tier genetic toxicology study
- Complete the two ongoing carcinogenicity studies (mouse and rat) with hydrocodone bitartrate

- Recommended Comments to Applicant

None

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/s/

ELLEN W FIELDS
01/31/2013